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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 067802-5008-US

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Application Number	Filed
10/599,980	3 April 2007

First Named Inventor: Roland REINER, et al.

Art Unit	Examiner
1623	Ganapathy KRISHNAN

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 48,574.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

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23 January 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Art Unit: 1623
Roland REINER *et al.*	Examiner: Ganapathy KRISHNAN
Appl. No. 10/599,980	Atty. Docket: 067802-5008-US
§371 Date: 3 April 2007	Confirmation No.: 7700
For: **Injectable Crosslinked And Uncrosslinked Alginates And The Use Thereof In Medicine And In Cosmetic Surgery**	Customer No.: 09629

PRE-APPEAL BRIEF CONFERENCE REQUEST

This communication is a Request for a Pre-Appeal Brief Conference for formal review of the rejection in the Office Action of 15 October 2009. Specifically, Applicants request formal review of the rejection of claims 23 and 27-49 as obvious over Marler *et al., Plast. Reconstr. Surg.*, 105:2049-2058 (2000) ("*Marler*"), in view of Bent *et al., Neurobiology and Urodynamics,* 20:157-165 (2001) ("*Bent*"), Agerup, (U.S. Patent No. 5,633,001) ("*Agerup*"), Vanderhoff *et al.*, (WO 1996/39464) ("*Vanderhoff*"), Mancini, *et al.*, J. Food Eng., 30:369-378 (1999) ("*Mancini*"), The Merck Index, 12th Ed. (1996) and Hawley's Chemical Dictionary (1997) ("Hawley's"). Applicants respectfully submit that (1) the Examiner's interpretation of the cited art is in clear error, (2) that the Examiner's failure to establish that the molecular weight of alginate is a result-effective variable is in clear error, and (3) that the Examiner's failure to establish a reasonable expectation of success is in clear error.

The sole rejection is an obviousness rejection, wherein the Examiner rejected claims 23 and 27-49 under 35 U.S.C. §103 as allegedly being unpatentable over the cited art. The rejection is, in essence, that the use of ionically cross-linked alginate of a specified molecular weight for tissue augmentation would be obvious to one of skill in the art in view of the cited references. It is Applicants' position that the cited references do not support a *prima facie* case of obviousness, because the cited references (1) fail to teach or suggest the claimed molecular weight of alginate, (2) fail to provide a reasonable expectation of success and (3) teach away from the claimed invention.

Ideally, injectable material used in tissue augmentation should possess long-term stability and have a low level of toxicity. The underlying problem in the art with using alginates in tissue augmentation is that the alginate material disappears or is degraded *in vivo* over a very short period of time, which, in turn, fails to provide long-term aesthetic effects. This lack of stability *in vivo* often requires repeated administration of the material, which can be problematic and can increase the risk of

treatment complications. These problems with the current state of the art have been presented and reiterated throughout prosecution.

The inventors have discovered that increasing the molecular weight of alginate increases its *in vivo* stability and, as an additional benefit, decreases its toxicity. The claimed methods use alginate of a specified molecular weight which exhibits significantly improved properties (in particular long term stability) as compared to the alginate material used in the methods disclosed in the cited art. None of the cited references teaches or suggests the use of higher molecular weight alginate to improve its *in vivo* stability.

The Examiner notes that primary reference upon which the obviousness rejection is based, *Marler*, does not suggest the use of alginates of a specified molecular weight for tissue augmentation. Moreover, *Marler* actually teaches away from the currently claimed methods. For example, *Marler* states that "calcium alginate was best able to support a specific soft-tissue construct when it was cross-linked after rather than before injection when it included cells." *Marler*, page 2056, left col., 2nd full para. (emphasis added). Indeed, the data in *Marler* would militate against using alginate that is cross-linked before injection ("pre-gelled alginate"). Specifically, the data in *Marler* (page 2053) shows that a pre-gelled alginate injection retains only about 30% of its volume 8 weeks post-injection. Applicants assert that one of skill in the art would not read *Marler* and then purposefully choose to inject a pre-gelled alginate to increase long term stability. They would do the opposite and first inject the alginate and then cross-link. In contrast to *Marler*, however, Applicants note that the claims require that the presently claimed methods require injection of cross-linked alginate, *i.e.,* the alginate is cross-linked prior to injection. Applicants assert, therefore, that *Marler* teaches away from the presently claimed methods and that the failure to recognize this teaching away is in clear error.

Bent does nothing to support the Examiner's position. For example, *Bent* states that "the [alginate] gel serves as a substrate for injectable delivery [of chondrocytes], and then degrades." *Bent*, page 158, 2nd full para. *Bent* desires the alginate to degrade so that "[t]he remaining cells then secrete a natural matrix, which maintains the volume of the original injection … ." *Id.* As one of skill would readily appreciate, if the alginate in *Bent* did not degrade, the secretion of the "natural matrix" would result in an increase in volume over the original injection volume. Applicants note again that the injected alginate in *Bent* is cross-linked with calcium, prior to injection, and that this pre-gelled alginate degrades. The loss of the pre-gelled alginate in *Bent* is consistent with the loss of the pre-gelled alginate in *Marler*.

Agerup does nothing to bolster the Examiner's position and teaches away from the claimed methods. As an initial matter, Example 2 of *Agerup* explicitly teaches away from the presently claimed invention by cross-linking after injection ("[t]he bolus was made harder by immediate follow-up of an injection of a 0.15M calcium chloride solution"). *Agerup*, Col. 3, ll. 60-61. Moreover, as the Examiner notes, *Agerup* only uses alginate as a carrier and not for tissue augmentation. This difference in the use for alginate must be taken into account in an obviousness rejection. In other words, the Office must address the question and make of record why one of skill would choose alginate as a stable tissue augmentation compound when *Agerup* teaches that alginate is only a carrier, and when both *Marler* and *Bent* explicitly teach that pre-gelled alginates degrade quickly. The Examiner fails to do so and this is clear error.

Vanderhoff also fails to support the Examiner's position and teaches away from the claimed methods. For example, *Vanderhoff*[1] explicitly emphasizes that covalent cross-linking is strongly preferred and, in fact, discourages the reader from using ionic cross-linking. Indeed, *Vanderhoff* states that "ionic bonds may be broken down by a change in external conditions, *e.g.*, by chelating agents. … Thus, the most preferred cross linking agent for use in the practice of the invention is one that forms covalent bonds … rather than ionic bonds." *Vanderhoff*, page 9, lines 30 – page 10, line 4. The Examiner also states that these problems with ionic cross-linking detailed in *Vanderhoff* apply only to calcium ions. *See Office Action of 15 Oct. 2009,* page 9. Applicants respectfully disagree and state that Vanderhoff does not limit its comments to calcium cross-linking. Instead, *Vanderhoff* makes a general statement about *ionic* cross-linking and then states that these problems can be surmounted using covalent cross-linking. Thus, *Vanderhoff* teaches away from the ionic bonds used in the claimed methods, which require ionically cross-linked alginate.

Applicants assert that the Examiner is failing to take into account all the claim limitations and is inaccurately summarizing the cited art. As discussed, *Marler* and *Bent* teach that pre-gelled alginate degrades quickly *in vivo*. Thus, the cited art does not teach that the alginates in *Marler* or *Bent* are stable *in vivo*. In addition, *Marler* in particular would force one to conclude that cross-linking alginate *after* injection could potentially solve stability problems and *Bent* could support this conclusion. *Vanderhoff*

[1] Applicants note that the Examiner underlines "sodium alginate" several times when discussing *Vanderhoff*, but it is unclear what the point of emphasis is. If the Examiner is attempting demonstrate than *Vanderhoff* teaches ions for cross-linking other than calcium, such as sodium, Applicants note that sodium alginate is simply the salt form of alginate, with an empirical formula of $NaC_6H_7O_6$, and the sodium part of sodium alginate is not the cross-linking agent.

could possibly build upon *Marler* and *Bent* and suggest to one of skill that using covalent bonding to cross-link alginate may also improve stability. Applicants assert that *Agerup* would not guide or direct one of skill in the art in any direction, since it mentions alginate as a carrier only in passing. To be clear, Applicants assert that one of skill in the art would not read *Marler, Bent, Vanderhoff* and *Agerup* and conclude that the molecular weight of alginate and ionically cross-linking prior to injection would solve *in vivo* stability problems.

The Examiner cites *Mancini*[2] in the obviousness rejection because *Mancini* uses alginate with a molecular weight of 200kDa in an *in vitro* mechanical assay. The entire disclosure of *Mancini* is focused on the mannuron/guluron ratio (M/G ratio) to increase mechanical strength. Yet, the Examiner simply extracts the molecular weight of alginate used in one experiment in *Mancini* and concludes that one of skill would inject alginates of this molecular weight for tissue augmentation. For example, the Examiner states that "[t]his means that alginates having molecular weights in the range as claimed … can be crosslinked to give a stable gel." *Office Action of 15 October 2009*, page 6. The Examiner also states that "Mancini … teaches cross-linking of alginates that have a molecular weight of 200kDa prior to crosslinking, to give stable gels." *Id.*, at 9. *Mancini*, however, does not inject alginates at any time, so *Mancini* can not possibly teach that alginates of 200kDa provide stable gels. To be clear, nothing in *Mancini* or of record actually explains why one would read *Mancini* and begin experimenting with molecular weight to increase *in vivo* stability. The Examiner fails to provide any explanation to support the assertions in the Office Action that one of skill would randomly choose a molecular weight of 200kDa, only mentioned in a single sentence in *Mancini*, and apply it to the teachings of *Marler, Bent, Agerup* and *Vanderhoff*. Put another way, the Examiner fails to establish that one of skill in the art would reasonably expect to successfully solve the problems shown in *Marler, Bent, Agerup* and *Vanderhoff* by reading *Mancini* and then choosing to focus on the molecular weight of alginate. This is clear error.

Thus, the cited art, other evidence and arguments of record fail to render obvious the claimed invention. Moreover, Applicants assert that the cited art would actually teach away from at least two elements of the claimed methods: ionic cross-linking and cross-linking prior to injection.

In response to the arguments presented, the Examiner states that "the cited art has not specifically mentioned any problems with stability if low molecular weight alginates are used … ." *Office Action of*

[2] Previously in prosecution, the Examiner attempted to make up for the lack of teaching of specific molecular weights of alginate by simply stating, incorrectly, that choice of molecular weight of alginate would be routine optimization. To refute this unsupported assertion, Applicants presented *Mancini* as an example to demonstrate that molecular weight was not recognized a result-effective variable that one would choose to optimize.

15 Oct. 2009, page 8. This statement is not the law of obviousness. Oddly, this statement seems to suggest that discoveries are obvious if the art is silent. If this were the case, virtually every new discovery would be obvious, because discoveries, by their very nature, are not discussed in the art prior to the discovery itself. Here, the inventors discovered that the molecular weight of alginate can affect stability *in vivo*. Applicants agree with the Examiner that none of the cited references mentions stability problems with low molecular weight alginate, which is precisely why the invention is not obvious.

As has been discussed at a personal interview and in written correspondence, Applicants' position is fortified by *Ex parte Whalen*, 89 USPQ2d 1078 (Bd. Pat. App. & Int. 2008). *Whalen* discusses an obviousness analysis when a claimed variable is not recognized in the art as a result-effective variable. Applicants assert that *Whalen* supports a conclusion of non-obviousness in the present case, because the Examiner fails to establish why one of skill would increase the molecular weight of alginate to increase *in vivo* stability. In addition, *Whalen* discusses a proper obviousness analysis when the cited art teaches away from the claimed invention, as is the case here, when it states:

> … when the prior art teaches away from the claimed solution as presented here …, obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.

Ex parte Whalen, 89 USPQ2d at 1084. Applicants assert that there is no apparent reason to modify the known methods that would result in the claimed methods; thus the presently claimed invention is not obvious.

Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Respectfully submitted,

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